

Protein-Protein docking studies on Magnesium chelatase of *Ulva fasciata* against the human TSHR protein

Abstract

The course and prognosis of hypothyroidism in humans are affected by the most common mutation in the hypothyroid protein, TSHR. To facilitate the potential mutant TSHR's interaction with *Ulva fasciata's* magnesium-chelatase, we utilize 3D *Insilico* drug docking approaches. The purpose of the entire research work is to introduce the seaweed protein against the human TSHR protein using *Insilico* protocols. The translated amino acid sequence and three-dimensional chemical compound were taken from the NCBI database to perform drug docking procedures. In post-docking tests, advanced 3D molecular visualization capabilities were utilized. In post-docking tests, advanced 3D molecular visualization capabilities were utilized. The findings of the docking investigation indisputably demonstrate that amino acid mutational sites are directly suppressed by magnesium chelatase. The H-bond interaction between TSHR and magnesium chelatase is shown in three dimensions utilizing concepts from molecular dynamics techniques. Ultimately, we found that *Ulva fasciata's* pharmaceutical ingredient, magnesium chelatase, aids in the treatment of hypothyroidism. Hence, we finally conclude that one of the main endocrine hormonal problems is hypothyroidism, and our research serves to demonstrate how well the seaweed *Ulva fasciata* works as a unique medicinal agent to treat this disorder.

Keywords: TSHR, *Ulva fasciata*, Protein –Protein Docking

Introduction

Thyroid-associated ophthalmopathy, also called Graves' orbitopathy (GO), is a relatively uncommon condition, with an incidence of 2.67–3.3 cases/100,000/year in females and 0.54–0.9 cases/100,000/year in males [1]. The incidence of GO varies depending on the

testing method used to diagnose GO, such as clinical signs and symptoms, physical examination, and imaging techniques. It affects approximately 25% to 50% of patients with Graves disease (GD). Eye discomfort, photophobia, hazy vision, increased tear production, and double vision are common signs of GO. One or both eyes may be affected by GO's periorbital oedema, exophthalmos, eyelid recession, and alterations in eye motility. A significant portion of GO patients—roughly 5–6%—have compressive optic neuropathy or potentially blinding corneal ulcerations; these individuals may go blind. Although GO can occur at any age, it most frequently affects women between 30 and 50 years old [2]. However, men and individuals who receive a diagnosis later in life tend to have more severe cases of GO [3]. Smoking, high cholesterol, thyroid dysfunction, radioiodine therapy, low thyroid peroxidase antibodies (TPOAbs), high thyrotropin receptor antibodies (TRAbs), and low thyroglobulin antibodies (TgAbs) are traditional risk factors for GO. High thyroglobulin (Tg) [4], a selenium deficit, an imbalance in the intestinal flora, and elevated levels of *Yersinia enterocolitica* and *Escherichia coli* in the digestive tract are new risk factors for GO [5].

The biological and chemical potential of seaweeds has been covered in other papers [6-9] [1-4]. Global seaweed aquaculture has generated about 30 million tons of fresh biomass in the last few decades, with a projected market value of over \$13.3 billion. More than 95% of the seaweed produced worldwide is farmed by *Laminaria/Saccharina* (35.4%), *Kappaphycus* and *Euclima* (33.5%), *Gracilaria* (10.5%), *Porphyra* (8.6%), and *Undaria* (7.4%) [10]. Seaweeds, therefore, represent a prospective millennium market with a number of social, economic, and ecological advantages [5, 6]. Coral reefs have lost up to 67% of their historical global range, making them one of the planet's most threatened ecosystems. Furthermore, human activity and the consequences of climate change threaten the remaining intact coral reef systems, as reported in a recent report by the Global Coral Reef Monitoring Network [11, 12]. Prior studies suggest that coral's secondary metabolites may have cytotoxic, anti-inflammatory, antifouling, and antimicrobial properties and benefits for bone repair and the nervous system [13, 14, 15, and 16].

Our investigation detailed the molecular interactions between the sea weed protein of *Ulva fasciata* and the human Thyroid Stimulating Hormone Receptor (TSHR). The final results clearly showed the mechanism of inhibition of magnesium chelatase with the Thyroid Stimulating Hormone Receptor.

Methodology

Target selection: Data from the NCBI Genpept database (YP_009220447.1 magnesium-chelatase (*Ulva fasciata*) and (AAI20973.1 TSHR protein (Human)) were utilized to conduct a molecular drug docking study. A powerful molecular visualization application called Discovery Studio was used to anticipate three-dimensional structures.

Protein Docking: HDock, an automated molecular drug docking service (<http://hdock.phys.hust.edu.cn/>), has been used in molecular drug docking research. [17]. Using a 3D molecular dynamics method, the molecular affinities of TSHR protein and YP_009220447.1 magnesium-chelatase (*Ulva fasciata*) in human hypothyroidism were ascertained.

Protein-Protein docking: Post-docking experiments were conducted with the Discovery Studio software. A thorough analysis of the three-dimensional image based on the docking score (3D H-bond/Electrostatic interactions) was carried out using the molecular dynamics concept.

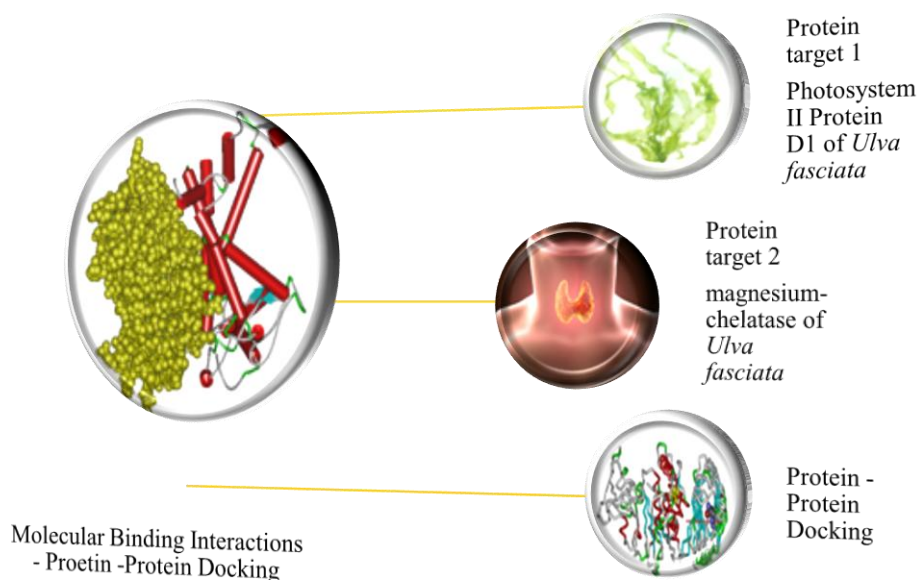


Figure 1: Diagrammatic representations of the overview of the *Insilico* research work

RESULTS and Discussion

>YP_009220447.1 magnesium-chelatase subunit ChlI (chloroplast) [*Ulva fasciata*]

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MSEKIELESRPVFPFTSIVGQEEMKLALILNVIDPKIGGVMVMGDRGTGKSTTVRALSDLLPDMKVVAND
PFNSDPNDPELMSDEVADKIKNNKTLEIETKKIPMIDLPLGATEDRVCGTIDMEKALTEGIKAFEPGLLA
SANRGILYVDEVNLLDDHLVDVLLDSAASGWNTVEREGISISHPARFILVSGNPPEGELRPQLLDRFGM
HAEIIRTVKEPDLRVQIVEQRAAFDSDPIEFRNNYSESQKTLSEKIVKARELLKEVDLNYEFRIKISQICS
ELNVDGLRGDIVTNRAAKALTAFEGRNEVTAQDIFRVIPLCLRHRRLRKDPLETIDSGDKVRDIFKKIFS
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Figure 2: Amino acid sequence of the sea weed, *Ulva fasciata*

>AAI20973.1 TSHR protein [*Homo sapiens*]

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MRPADLLQLVLLLDLPRDLGGMGCSPPCECHQEEDFRVTCKDIQRIPSLPPSTQTLKLIETHLRITPISH
AFSNLNPNISRIYVSIDVTLQQLESHSFYNLSKVTHIEIRNTRNLTYIDPDALKELPLLKFLGIFNTGLKM
FPDLTKVYSTDIFFILEITDNPYMTSIPVNAFQGLCNETLTLKLYNNGFTSVQGYAFNGTKLDAVYLNKN
KYLTVIDKDAFGGVYSGPSLL
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Figure 3: Amino acid sequence of human TSHR protein

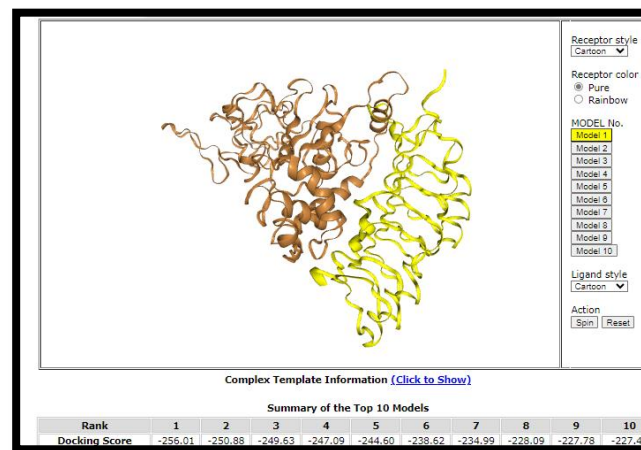


Figure 4: Complex form of human TSHR protein and YP_009220447.1 magnesium-chelatase of *Ulva fasciata* viewed using H-Dock server with respective binding scores.

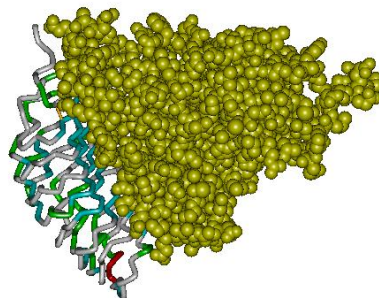


Figure 5: Complex form of human TSHR protein and YP_009220447.1 magnesium-chelatase of *Ulva fasciata* viewed using Discovery Studio Software. Yellow coloured structure represents the TSHR protein.

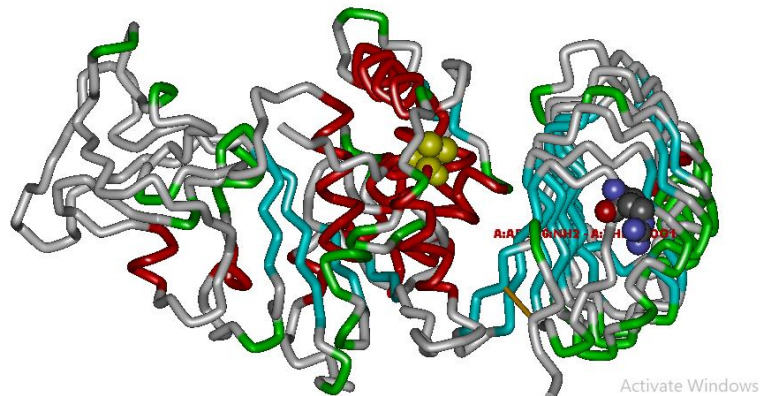


Figure 6: 3D Complex form of human TSHR protein and magnesium-chelatase of *Ulva fasciata* viewed using Discovery Studio software (Binding Interaction Mode).

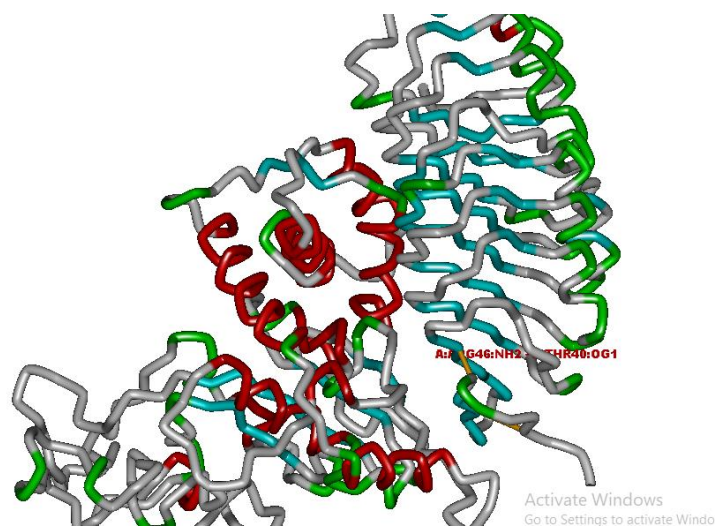


Figure 7: 3D Complex form of human TSHR protein and magnesium-chelatase protein of *Ulva fasciata* viewed using Discovery Studio software (Binding Interaction Mode with respective amino acid labels/positions).

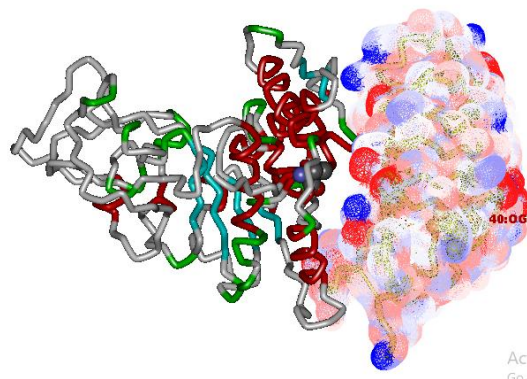


Figure 8: 3D Complex form of human TSHR protein and magnesium-chelatase protein of *Ulva fasciata* viewed using Discovery Studio software (Amino acids interacting at Domain and Motif).

The amino acid sequences corresponding to the gene-coded proteins of photosystem II protein D1 (*Ulva fasciata*) and TSHR are 349 aa and 231 aa, respectively (Fig: 1 and 2). In our research work, we use the potential inhibitor derived from algae (*Ulva fasciata*).

Marine macroalgae are eukaryotic, macroscopic, multicellular, photosynthetic organisms that are classified as belonging to the order Plantae. Seaweed is another name for these creatures. In addition to the seabed or solid rock strata beneath it, these salt-loving marine plants can also be found on the surfaces of rocks, corals, shells, pebbles, and other plants. In oceanic places where light is most abundant, marine algae typically thrive in the tidal and subtidal zones. Because of their easy response to physiological changes by creating stress-tolerant chemicals, they can endure extreme temperatures, cold temperatures, UV radiation, salinity, and desiccation. A multitude of primary and secondary metabolites are produced by them as a result of their survival. Numerous physiologically active substances with a range of therapeutic advantages can be found in marine algae [18, 19].

The complex form of the TSHR protein retrieved via the H-Dock server and photosystem II protein D1 have a 3D docking score of -256.01 kcal/mol , (Fig :3) as illustrated in Fig. (1). Using Discovery Studio software, the H-bond interactions between photosystem II protein D1 and the TSHR protein are displayed in detail (Fig: 4, 5, 6, 7, 8). It is clear from this image that the TSHR protein and the photosystem II protein D1 protein structure have interacted non-covalently. Therefore, it may be said that, as demonstrated by

earlier research, the TSHR protein will be downregulated. Our docking studies are consistent with a number of prior investigations [17, 18, 19, 20, 21, 22].

Our retrieved protein's functional domain area is the *Ulva fasciata* 46 SER (44-51) *ATP/GTP-binding site motif A (P-loop* (PS00017). Our research demonstrates that gentamicin, an antibiotic, interacts directly with the domain areas. Our study unequivocally demonstrated that the following amino acids are present at the drug-protein binding region: ARG:46,THR:40,ARG:241,GLU:34,TYR:244,GLN:33

Conclusion

Our research clearly shows that the human hypothyroidism protein, TSHR, and the seaweed protein interact. Our unambiguous docking data clearly show that the *Ulva fasciata* magnesium-chelatase binds well to the functional domain area of the TSHR protein. The binding connection between magnesium-chelatase and TSHR protein, as determined by docking scores, defines the H-bond interaction precisely. Consequently, we draw the conclusion that the protein found in *Ulva fasciata* seaweed serves as a potential endocrinological drug that alleviates the symptoms of hypothyroidism in people. Our Insilico work unequivocally demonstrates that magnesium-chelatase may have pharmacological effects on the human TSHR protein.

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Competing interests

The authors disclose that there are no conflicts of interest.

References

1. Bartalena, L., Kahaly, G. J., Baldeschi, L., Dayan, C. M., Eckstein, A., Marcocci, C., Marinò, M., Vaidya, B., Wiersinga, W. M., & EUGOGO † (2021). The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *European journal of endocrinology*, 185(4), G43–G67.
2. Bartalena L. (2013). Diagnosis and management of Graves disease: a global overview. *Nature reviews. Endocrinology*, 9(12), 724–734.
3. Weiler D. L. (2017). Thyroid eye disease: a review. *Clinical & experimental optometry*, 100(1), 20–25.
4. Khamisi, S., Lundqvist, M., Emadi, P., Almby, K., Ljunggren, Ö., & Karlsson, F. A. (2021). Serum thyroglobulin is associated with orbitopathy in Graves' disease. *Journal of endocrinological investigation*, 44(9), 1905–1911
5. Cao, J., Su, Y., Chen, Z., Ma, C., & Xiong, W. (2022). The risk factors for Graves' ophthalmopathy. *Graefe's archive for clinical and experimental ophthalmology* =

Albrecht von Graefes Archiv für klinische und experimentelle Ophthalmologie, 260(4), 1043–1054.

6. Kalasariya, H. S., Yadav, V. K., Yadav, K. K., Tirth, V., Algahtani, A., Islam, S., Gupta, N., & Jeon, B. H. (2021). Seaweed-Based Molecules and Their Potential Biological Activities: An Eco-Sustainable Cosmetics. *Molecules (Basel, Switzerland)*, 26(17), 5313.
7. Lomartire, S., & Gonçalves, A. M. M. (2022). An Overview of Potential Seaweed-Derived Bioactive Compounds for Pharmaceutical Applications. *Marine drugs*, 20(2), 141.
8. Gomez-Zavaglia, A., Prieto Lage, M. A., Jimenez-Lopez, C., Mejuto, J. C., & Simal-Gandara, J. (2019). The Potential of Seaweeds as a Source of Functional Ingredients of Prebiotic and Antioxidant Value. *Antioxidants (Basel, Switzerland)*, 8(9), 406.
9. Salehi, B., Sharifi-Rad, J., Seca, A. M. L., Pinto, D. C. G. A., Michalak, I., Trincone, A., Mishra, A. P., Nigam, M., Zam, W., & Martins, N. (2019). Current Trends on Seaweeds: Looking at Chemical Composition, Phytopharmacology, and Cosmetic Applications. *Molecules (Basel, Switzerland)*, 24(22), 4182.
10. Sultana, F. *et al.* (2023) ‘Seaweed farming for food and nutritional security, climate change mitigation and adaptation, and women empowerment: A Review’, *Aquaculture and Fisheries*, 8(5), pp. 463–480. doi:10.1016/j.aaf.2022.09.001.
11. Ashkenazi, D. Y., Figueroa, F. L., Korbee, N., García-Sánchez, M., Vega, J., Ben-Valid, S., Paz, G., Salomon, E., Israel, Á., & Abelson, A. (2022). Enhancing Bioproducts in Seaweeds via Sustainable Aquaculture: Antioxidant and Sun-Protection Compounds. *Marine drugs*, 20(12), 767.

12. Devlin M. J. (2022). Coral reefs: The good and not so good news with future bright and dark spots for coral reefs through climate change. *Global change biology*, 28(15), 4506–4508.
13. Yan, X., Liu, J., Leng, X., & Ouyang, H. (2021). Chemical Diversity and Biological Activity of Secondary Metabolites from Soft Coral Genus *Sinularia* since 2013. *Marine drugs*, 19(6), 335.
14. Souza, C. R. M., Bezerra, W. P., & Souto, J. T. (2020). Marine Alkaloids with Anti-Inflammatory Activity: Current Knowledge and Future Perspectives. *Marine drugs*, 18(3), 147.
15. Alves, C., & Diederich, M. (2021). Marine Natural Products as Anticancer Agents. *Marine drugs*, 19(8), 447.
16. Sheehy, E. J., Lemoine, M., Clarke, D., Gonzalez Vazquez, A., & O'Brien, F. J. (2020). The Incorporation of Marine Coral Microparticles into Collagen-Based Scaffolds Promotes Osteogenesis of Human Mesenchymal Stromal Cells via Calcium Ion Signalling. *Marine drugs*, 18(2), 74.
17. Yan, Y. *et al.* (2020a) ‘The HDOCK server for integrated protein–protein docking’, *Nature Protocols*, 15(5), pp. 1829–1852. doi:10.1038/s41596-020-0312-x.
18. Park, B. S., & Li, Z. (2022). Taxonomy and ecology of marine algae. *Journal of Marine Science and Engineering*, 10(1), 105.
19. Jimenez-Lopez, C., Pereira, A. G., Lourenço-Lopes, C., Garcia-Oliveira, P., Cassani, L., Fraga-Corral, M., Prieto, M. A., & Simal-Gandara, J. (2021). Main bioactive phenolic compounds in marine algae and their mechanisms of action supporting potential health benefits. *Food chemistry*, 341(Pt 2), 128262.

20. Houseini, S. T., Nemati, F., Sattari, A., Azadeh, M., & BishehKolaei, R. (2023). Design of crRNA to Regulate MicroRNAs Related to Metastasis in Colorectal Cancer Using CRISPR-C2c2 (Cas13a) Technique. *Cell journal*, 25(5), 354–362.
21. Astalakshmi, P. *et al.* (2023a) ‘Identification of the efficiency of pentane on the bacterial and insecticide proteins of *Aedes aegypti* and *aeromonas hydrophila* by Insilico Methods’, *International Journal of Mosquito Research*, 10(3), pp. 47–53. doi:10.22271/23487941.2023.v10.i3a.678.
22. Astalakshmi, P. *et al.* (2023b) ‘In silico study on hexadecanoic acid against the outer membrane protein transport protein of *Culex quinquefasciatus* and *aeromonas hydrophila*’, *International Journal of Mosquito Research*, 10(4), pp. 07–14. doi:10.22271/23487941.2023.v10.i4a.680.
23. G, N. and V, P. (2023) ‘Identification of a plant derivative (*Hibiscus cannabinus*) for Mosquito (*anopheles darlingi*) control using in silico protein-protein docking techniques’, *International Journal of Mosquito Research*, 10(4), pp. 25–29. doi:10.22271/23487941.2023.v10.i4a.683.
24. Maithreyee S,* and Prabha V,(2023) ‘Molecular Interactions between Anti-inflammatory Drug with Colorectal Cancer (MSH2) Protein Using In-silico Studies’. *Solovyov Studies ISPU*. 71(10), 171-186.
25. Nijanthi, P., S, S. and Munivelan, B. (2023) ‘Molecular dynamics studies on the arginine kinase protein of *Aedes sollicitans*: Against the natural chemical compound, Gedunin’, *International Journal of Mosquito Research*, 10(2), pp. 10–14. doi:10.22271/23487941.2023.v10.i2a.665.
26. Suganya, M. and Devi, G.B. (2023) ‘Heavy Metal (PB) bioaccumulation study in *Eisenia fetida* and in the larvae of *anopheles gambiae* complex using in silico drug

docking protocols', *International Journal of Mosquito Research*, 10(6), pp. 45–51.

doi:10.22271/23487941.2023.v10.i6a.716.